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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,182	03/23/2001	Darwin J. Prockop	53844-5019	5852

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EXAMINER

FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,182	PROCKOP ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 4-8 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment filed May 19, 2004 (hereinafter referred to as "the response") has been entered. Claims 1 and 9 have been amended.

Claims 1-10 remain pending in the instant application.

Claims 4-8 and 10 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the response filed October 23, 2003. The elected invention is drawn to a population of small and rapidly self-renewing stem (RS) cells.

Accordingly, Claims 1-3 and 9 are examined herein.

The rejection of Claims 1-3 and 9 under 35 U.S.C. 102(a) as being anticipated by Colter et al. (2000) is withdrawn in view of the amendments to the claims. At page 8, paragraph 3 of the response, Applicants assert that Colter does not teach a homogenous population of cells, but rather teaches a heterogeneous population of cells. Applicants point to page 3214, column 2, where the reference states that **two** populations of cells were seen in stationary culture, that most of the cells were large, that there was a minor population of small, agranular cells, and that about 98% of **both** populations were viable. The Examiner agrees that Colter teaches a heterogeneous population of cells.

The rejection of Claims 1-3 and 9 under 35 U.S.C. 102(b) as being anticipated by DiGirolamo et al. (1999) is withdrawn in view of the amendments to the claims. As amended, the claims now recite that the cell population must be "homogenous" and the cell cultures taught by DiGirolamo et al. are heterogeneous cell populations.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a homogenous population of small and rapidly self-renewing stem (RS) cells, wherein the cells within said population express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2). The specification discloses that the cells referred to as RS cells are isolated from human bone marrow, although the claims are not limited to human cells.

As amended the claims newly recite the limitation of “a homogenous population” of small and rapidly self-renewing stem cells (RS). However, the specification does not teach how to obtain a “homogenous” population of RS cells expressing one or more of the polypeptides recited in the claims. While the specification does not explicitly define an RS cell or a “small and rapidly self-renewing stem cell”, it does reveal that the term refers to a **heterogeneous** population of cells (p. 8, lines 28-29). As is evident from the specification, the term “RS cells” refers to a **mixed population** of cells and the specification does not provide specific guidance for isolating a single cell type from within that mixed population so as to produce a purified and homogeneous population of cells that express one or more of the polypeptides recited in the claims. On the contrary, the specification explicitly teaches that “even the sub-population defined as RS cells

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were heterogeneous since they did not stain uniformly for several surface epitopes” (page 8, lines 28-29). For example, Table 1 discloses that some RS-1 cells express CD4, while some do not and further that some RS-2 cells express CD4, while some do not. The specification goes on to say that “[t]herefore, it will be of interest to further sub-fractionate the RS cell population and determine the potentials of the sub-populations for multilineage differentiation and for engraftment to specific tissues” (page 9, lines 1-3). The specification further states that “FACS analyses distinguished two subtypes of RS cells: Small and agranular cells (RS-1 cells) seen in stationary and late-log phase cultures, and small granular cells (RS-2 cells)” (page 7, lines 15-17). Thus, it is clear that the disclosed cell compositions are not homogeneous cell populations, but rather represent mixed populations of cells requiring further fractionation to produce homogeneous cell populations. The specification does not provide specific guidance for carrying out this further fractionation.

Given the limited guidance provided in the specification for generating homogeneous cell populations as recited in the claims, the lack of applicable working examples for obtaining homogeneous cell populations, and the unpredictability for developing purification protocols for separating the desired cell type from unwanted cell types, undue experimentation would have been required for one skilled in the art to produce the claimed cell compositions.

Written Description

Claims 1-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

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Applicants are reminded that the written description requirement is severable from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), *cert. denied*, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

The specification does not describe a homogeneous population of RS cells.

This is **not** a new matter rejection. Although the specification contemplates a homogeneous population of cells, it does not describe the claimed homogeneous population of RS cells because the specification only describes a heterogeneous population of RS cells. The term “RS cells” is clearly used in the specification to refer to a heterogeneous mixture of cells in a manner analogous to the way “blood cells” would be used to refer to a heterogeneous mixture of cells.

As amended, the claims are now directed to a homogenous population of small and rapidly self-renewing stem cells (RS), wherein the cells within said population express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2). However, the specification describes only a **heterogeneous** cell population, not a homogenous cell population.

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At page 6 of the response, Applicants assert that support for a homogenous population of RS cells is found at page 1, line 24. However, at page 1, line 24, the specification only discusses a desire to generate “large numbers of homogeneous cells”; it does not actually disclose or describe a homogeneous population of cells. A desire to obtain a homogeneous population of cells is not itself a description of the particular homogeneous population of cells now being claimed. Applicants further assert that, at page 6, line 14, the specification teaches a method of preparing a purified fraction of RS cells from a mixture of cells containing larger, mature marrow stromal cells. Applicants conclude that a homogenous population of RS cells is fully supported by the as-filed specification. While such a cell population is contemplated, the Examiner does not agree that there is a written description of a homogeneous population of RS cells. Teaching a method for **fractionating** cells does not automatically lead to a pure, homogenous fraction of RS cells. For example, one can readily fractionate CD34⁺ cells from a mixture comprising both CD34⁺ cells and CD34⁻ cells. That does not mean that the CD34⁺ fraction is homogeneous or pure. Many different cell types are CD34⁺. In the instant case, there is no question that the RS cell fraction is heterogeneous, because the specification readily admits that “even the sub-population defined as RS cells were heterogeneous since they did not stain uniformly for several surface epitopes” (page 8, lines 28-29).

Thus, it is concluded that the written description requirement is not satisfied for the claimed homogenous population of RS cells recited in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 9 is indefinite in its recitation of “said population of MSC” and “said MSC cell population” because the phrases lack antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 9 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bruder et al. (1997, J. Cell. Biochem. 64: 278-294).

The claims are directed to a homogenous population of small and rapidly self-renewing stem (RS) cells, wherein the cells within said population express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2). The specification discloses that the RS cells were isolated from human bone marrow and comprise human mesenchymal stem cells.

Bruder et al. (1997) disclose isolated human mesenchymal stem cells (MSC). Bruder further discloses the preparation of a homogeneous population of spindle-shaped, rapidly dividing cells (page 290, column 2, paragraph 1). The reference further discloses that the rapidly dividing cells can be maintained in the undifferentiated state, but still retain the capacity to differentiate along the osteogenic lineage when exposed to Osteogenic Supplements (page 290, column 2, paragraph 1). Thus, the cells retain the MSC phenotype. Given that the RS cells claimed comprise human mesenchymal stem cells, as disclosed in the instant specification, one of skill in the art would recognize that the claimed cells are identical to the cells disclosed by Bruder et al. Marker polypeptides are routinely used to identify a particular cell type. Therefore, since the expression of particular markers is considered an inherent property of a particular cell type, the

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particular polypeptides mentioned in the claims, such as FLK-1, TRK, transferrin receptor, and annexin II are considered an inherent property of a known cell type. Human mesenchymal stem cells are already known in the art and further characterization of marker polypeptides expressed by mesenchymal stem cells does not make the known cell type novel or patentable. In the decision of *In re Spada*, 15 USPQ2d 1655 (CAFC 1990) the court points out that discovery of a new property or use of a previously known composition, even if unobvious from prior art, cannot impart patentability to claims to known compositions. Mesenchymal stem cells constitute “a previously known composition.” Likewise, the homogeneous population of human mesenchymal stem cells is clearly “a previously known composition” because Bruder discloses it.

Mesenchymal stem cells necessarily express mesenchymal stem cell polypeptides/markers.

However, disclosing the identity of those particular markers or disclosing a protein expression profile of a known cell type does not make the known cell type suddenly new. Rather such a disclosure only represents further characterization of a composition already known in the art.

Thus, the claimed invention is disclosed in the prior art.

At page 5 of the response, Applicants cite *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) for teaching that “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” Applicants assert that Bruder must describe each and every element of claims 1-3 and 9, in order to anticipate these claims under 35 U.S.C. § 102(b), and this reference does not. In response to these comments, it is noted that Bruder teaches each and every element of the claimed cell population. First, Bruder teaches a homogeneous population of human mesenchymal stem cells. Second, Bruder teaches that the cells can be maintained and expanded in an undifferentiated state, while retaining the capability to differentiate along the osteogenic lineage when provided with the appropriate inductive cues. Thus, the cells of the homogeneous population clearly exhibit the MSC phenotype. Third, Bruder teaches that the human

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mesenchymal stem cells were isolated from human bone marrow aspirated from the iliac crest. The bone marrow cells were fractionated on a density gradient and the hMSC-enriched low density fraction was collected, rinsed with control medium, plated at 10^7 nucleated cells per 60 cm^2 dish in control medium, and cultured at 37°C in a humidified atmosphere containing 5% CO_2 . Nonadherent cells were removed on day 3 at the time of the first medium change, and fresh control medium was changed twice weekly thereafter. Fourth, as discussed in detail above, mesenchymal stem cell polypeptides/markers expressed by human MSCs are an inherent characteristic of hMSCs.

The MPEP states that the “express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103.” MPEP § 2112. Also see the decision of *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) which states that “[t]he inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.” The MPEP further emphasizes that the “inherent feature need not be recognized at the time of the invention” (MPEP § 2112).

MPEP § 2112 explicitly states the following:

“SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

“The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).”

The MPEP further teaches that “once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference.” MPEP § 2112. In the instant case, no evidence has been presented to show that the prior art product does not necessarily or inherently possess the characteristics of the claimed cell population.

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At page 6 of the response, Applicants argue that, because the bone marrow obtained in Bruder comprises both adherent and non-adherent cells, the cells of Bruder are a mixed population of cells. However, this is merely the starting material of Bruder; it is not the cell population cited in the rejection. The cell population being cited in the rejection is the homogeneous population of rapidly dividing cells referred to at page 290, column 2, paragraph 1.

At page 6 of the response, Applicants argue that Bruder does not teach that “the adherent hMSCs can further be separated into at least two more population of cells: 1) small and rapidly self-replicating cells (RS cells) and 2) larger, mature marrow stromal cells as claimed in the present application.” However, Bruder need not teach this element because the claims under examination are not directed to a cell population comprising these 2 separable cell populations. On the contrary, the claims are directed to a “**homogenous** population” of RS cells and Bruder teaches a homogeneous population of rapidly dividing cells.

At page 6 of the response, Applicants assert that the present invention relates to the novel discovery that the cells of the present invention express unique polypeptides and methods of isolating these cells using the unique polypeptides. This is not an accurate statement of the present invention. The “present invention” is whatever is now claimed. The claims are not directed to methods of isolating cells. Furthermore, reciting cell characteristics, such as polypeptides expressed by the cells, in claims directed to cell populations, does not make **known cell compositions** novel or patentable.

At page 7 of the response, Applicants assert that Bruder does not teach the polypeptides recited in the claims as features that characterize the cell disclosed therein. Applicants conclude that Bruder cannot anticipate the present invention because Bruder does not disclose each and every element of the claimed invention. Applicants’ conclusion is wrong because the polypeptides expressed by a particular cell type are clearly an inherent property of the cell type. If they were not, scientists could not use cell surface markers and intracellular markers to

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distinguish one cell type from another. Thus, by disclosing the same cell population that is recited in the claims, Bruder does disclose each and every element of the claimed invention.

Claims 1-3 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Pittenger et al. (1999, Science 284: 143-147).

Pittenger et al. (1999) disclose an isolated population of homogeneous human mesenchymal stem cells from bone marrow taken from the iliac crest (page 143, column 3). The legend to Figure 1 states that at 14 days, the cells were 95 to 99% homogeneous and were negative for reactivity to antigens CD14, CD34, or CD45. The figure legend also states that homogeneity and reproducibility of the isolation procedure was demonstrated by flow cytometry (see Figure 1D). At page 144, column 1, the reference states that the "isolated cultured mesenchymal cells comprised a single phenotypic population (95 and 98% homogeneous at passages 1 and 2, respectively) by flow cytometric analysis of expressed surface antigens." The cells were uniformly positive for SH2, SH3, CD29, CD44, CD71, CD90, CD106, CD120a, CD124, and many other surface proteins (page 144, column 1). CD71 is another name for transferrin receptor. Thus, it is clear that the cells disclosed by Pittenger meet the limitation of Claim 1, which recites that the cells "express one or more polypeptides selected from the group consisting of VEGF receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and annexin II (lipocortin 2)." The expression of the particular polypeptides, such as FLK-1, TRK, transferrin receptor, and annexin II is considered an inherent property of a known cell type. In the decision of *In re Spada*, 15 USPQ2d 1655 (CAFC 1990) the court points out that discovery of a new property or use of a previously known composition, even if unobvious from prior art, cannot impart patentability to claims to known compositions.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowed.

This application contains claims 4-8 and 10 drawn to an invention nonelected without traverse in the reply filed on October 23, 2003. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER